

# Practical Perspectives for Management of Thyroid Nodules with Atypical Needle Biopsy



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## Abstract

The purpose of this mini-review is to review the current recommendations in the management of atypia of undetermined significance or follicular lesion of undetermined significance (AUS or FLUS). We will discuss the role of clinical and ultrasound which can be used to decide if a timely or aggressive intervention is necessary or not. Furthermore, we will address the clinical practice guidelines and determination of the course of action after initial FNA shows atypia. Lastly, the new approach of using molecular markers to help rule-out/rule-in malignancy will be addressed.

**Keywords:** Atypia of undetermined significance (AUS); follicular lesion of undetermined significance (FLUS); intermediate cytology; fine needle aspiration; thyroid nodule; thyroid cancer; thyroid ultrasound; molecular genetic tests; practice guidelines

**Abbreviations:** AACE: Association of American Clinical Endocrinologists; ATA: American Thyroid Association; AUS: Atypia of Undetermined Significance; BTA: British Thyroid Association; FLUS: Follicular Lesion of Undetermined Significance; FNA: Fine Needle Aspiration; NPV: Negative Predictive Value; PPV: Positive Predictive Value

## Introduction

Over the past 40 years the incidence of thyroid cancer has nearly tripled, from 4.9 to 14.3 per 100,000 individuals, however the mortality rate has remained unchanged (approximately 0.5 deaths per 100,000) [1]. FNA is the most accurate, cost-effective and commonly used method for evaluating thyroid nodules [2]. The Bethesda system for reporting thyroid cytopathology

2009 provides the following diagnostic categories to classify thyroid nodule cytology [3]. Diagnostic categories includes non-diagnostic or unsatisfactory, atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN), suspicious for malignancy, and malignant.

**Table 1:** The AUS interpretation as outlined by the Bethesda System for Reporting Thyroid Cytopathology. Given the diversity in this category only the most common ones are listed.

Prominent population of microfollicles that does not otherwise fulfill the criteria for "follicular neoplasm/suspicious for follicular neoplasm."	Predominance of Hürthle cells in a sparsely cellular aspirate with scant colloid.	The interpretation of follicular cell atypia is hindered by sample preparation artifact.
Moderately or markedly cellular sample is composed of a virtually exclusive population of Hürthle cells, yet the clinical setting suggests a benign Hürthle cell nodule.	Focal features suggestive of papillary carcinoma, including nuclear grooves, enlarged nuclei with pale chromatin, and alterations in nuclear contour and shape in an otherwise predominantly benign-appearing sample.	Cyst-lining cells that may appear atypical owing to the presence of nuclear grooves, prominent nucleoli, elongated nuclei and cytoplasm, and/or intranuclear cytoplasmic inclusions in an otherwise predominantly benign appearing sample.
Minor population of follicular cells show nuclear enlargement, often accompanied by prominent nucleoli,	Atypical lymphoid infiltrate (in which a repeated aspirate for flow cytometry is desirable), but the degree of atypia is insufficient for the general category "suspicious for malignancy."	Not otherwise categorized

Most recently non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has been added to the list of the pathological diagnoses of thyroid nodules to avoid cancer terminology. NIFTP is not a benign lesion but it is also not an overt cancer since it carries an extremely low malignant potential, analogous to the “in situ” cancer. Therefore, diagnostic lobectomy would be adequate for diagnosis and treatment of NIFTP lesion without the need of total or completion thyroidectomy, radioactive iodine ablation, or intensive monitoring [4].

AUS/FLUS are classified as one of the intermediate cytologies and is obtained in 3-10% of thyroid FNA [5,6] (Table 1). Although AUS/FLUS are found in a minority of thyroid FNA it has created a diagnostic dilemma given its estimated 5-15% risk of malignancy which can be worrisome to patients [3].

When presented with a diagnosis of AUS/FLUS the next step in management usually involves continued surveillance versus an invasive procedure. Therefore this usually leads to a repeat FNA, Core needle biopsy ± flow cytometry, or diagnostic surgery which can lead to further patient morbidity. Experience with historical/physical examination features suggestive of malignancy and the use of noninvasive techniques has contributed to improvements in the safety and cost-effectiveness of management of patients with thyroid nodules in general [7].

## Clinical Practice Guidelines for atypia of undetermined significance or follicular lesion of undetermined significance (AUS or FLUS)

The most recent ATA guidelines 2015 recommends that after consideration of worrisome clinical and sonographic features, investigations such as repeat FNA or molecular testing may be used to supplement malignancy risk assessment [2]. The AACE guidelines 2016 recommends consideration of conservative management or repeat FNA for further cytologic assessment but does not recommend either in favor or against the determination of molecular markers for routine use in this category [8].

## Determination of course of action after initial FNA shows AUS/FLUS

### Clinical features

Although the history and physical examination cannot accurately predict malignancy, the acquisition of this information is vital to deciding on the course of action. Pertinent personal history includes neck area irradiation. Long-term survivors of childhood cancers who received radiotherapy to the head, neck or upper thorax are known to have not only an increased risk of thyroid nodules but are also at increased risk of developing thyroid cancer [9,10]. However, further evaluation should be similar to the standard of care of individuals with a thyroid nodule in the general population [11].

Well-differentiated thyroid cancer accounts for 95% of thyroid malignancies, and 5% of these patients will have familial

disease [11,12]. Therefore, family history of a first degree relative with familial thyroid cancer or thyroid cancer syndrome for example PTEN hamartoma tumor syndrome [Cowden's disease], familial adenomatous polyposis, Carney complex, Werner syndrome/progeria, or multiple endocrine neoplasia (MEN) type 2 should be obtained. Physical examination findings which may lead to suspicion of malignancy includes a rapid change in size of the nodule, a nodule that is hard on palpation or fixed to surrounding tissue and abnormal cervical lymphadenopathy.

### Laboratory

For nodules that have returned with the categorization of AUS/FLUS, it is beneficial to review both thyrotropin testing and ultrasound of thyroid gland and lateral neck. It is well established that a subnormal TSH would warrant not a repeat FNA but instead warrant a radionuclide thyroid scan to exclude a hyper functioning, i.e. “hot” nodule because hyper functioning nodules are rarely malignant. A hot nodule will show hyperplastic follicular cells with nuclear enlargement, often accompanied by prominent nucleoli on cytology which makes the cells look atypical. A serum TSH in the normal or higher range is however associated with an increased risk of malignancy in a thyroid nodule [2,13].

### Ultrasound

Comparison of the 2016 AACE, 2015 ATA, and 2014 BTA thyroid nodule ultrasound classification systems reveals the following ultrasound features that are associated with an increased risk of malignancy found in all three classification systems include nodule height greater than its width, hypoechogenicity, solid nodule structure, the presence of micro calcifications or disruptive rim calcifications, and irregular margins (which can be defined as infiltrative, microlobulated, or spiculated). The AACE and BTA also include pathologic lymphadenopathy as a feature of malignancy. Whereas the AACE and ATA include extra thyroidal growth and invasion as an additional risk category [2,8,14,15]. The combination of two more features increases the specificity for malignancy but has low ultrasound sensitivity for cancer [8].

Ultrasonographic features that invoke intermediate or equivocal suspicion for malignancy include indeterminate hyperechoic spots, slightly hypoechoic or homogenous nodules, intranodular or mixed/central vascularity, and absent halo sign, that is, periphery of nodule is surrounded by echo poor tissue [2,8,14,15]. Finally, ultrasonographic features that suggest low risk or benign nature include nodules with halos, isoechoic, spongiform, mildly hyperechoic nodules, or purely cystic nodules. [2,8,15].

### Molecular markers

The review article by Lathief et al. [16] highlights the ATA 2015 recommendation for molecular testing (strong recommendation, low quality evidence) to occur after counseling patients on benefits and limitations of testing and

the AACE 2016 recommendation that molecular testing to complement cytologic evaluation (grade A). Testing for detection of BRAF, RET/PTC, PAX8/PPRG, and RAS mutations are also recommended (grade B). Overall, thyroid molecular testing can be a useful tool when combined with clinical and ultrasound risk

assessment of indeterminate thyroid cytology. (Table 2) outlines four commercially available genetic tests for molecular testing, adapted from our review article on advances and practical use of the molecular markers for thyroid cancer [16].

**Table 2:** Overview of 4 commercially available genetic tests for atypical (AUS/FLUS) thyroid cytology.

Test	Afirma	ThyroSeqverion 2 Next Generation Sequencing	ThyGenX/ ThyraMIR	Rosetta GXReveal
Company	Veracyte	University of Pittsburgh Medical Center through CBL Path	Interspace Diagnostics	Rosetta Genomics
Methods	Based on mRNA (gene expression); classified as benign or malignant	Next-generation sequencing which detects 14 gene mutations (AKT1, BRAF, CTNNB1,GNAS, HRAS, KRAS, NRAS,PIK3CA, PTEN, RET, TP53, SHR,TERT, and EIF1AX and > 42 gene rearrangements (RET-PTC, PAX-8/PPARG etc)	ThyGen X: Uses PCR for detection of 7 common gene mutations (BRAF, RAS, NRAS, and KRAS) and rearrangements (RET-PTC1, RET-PTC3, and PAX8-PPARG) first with sequence-specific probes. If initial mutation panel is negative then further testing for 10-gene micro RNA classifier (ThyraMIR: expression analysis) will be done.	Micro RNA-based diagnostic assay. First thyroid test that works on stained FNA smears containing at least 60 cells for analysis
Strengths	High NPV: AUS/FLUS- 95% “ Rule Out “Test Identifies MTC with MTC gene classifier	High PPV 68-72% “ Rule in test” High NPV 96 % “ Rule Out” assay Risk stratification based on mutation and prognostic value	High NPV 94 % High PPV 74 %	High NPV 91% Rule out test
Limitations	Low PPV AUS/FLUS- 38% High false positive results	Newer assay with limited experience	New assay with limited experience	Low PPV 59%

**\*Abbreviations:** AUS: Atypia of Undetermined Significance; FLUS: Follicular Lesion of Undetermined Significance; MTC: Medullary Thyroid Cancer; NPV: Negative Predictive Value; PPV: Positive Predictive Value

**Conclusion**

Management options for an initial atypical thyroid nodule biopsy like AUS/FLUS include observation, repeat FNA, diagnostic lobectomy or thyroidectomy. Laboratory, clinical and ultrasound findings provide valuable information that can be incorporated into the decision making process. Molecular testing which are described briefly in this review should be used as an adjunct to these findings and may serve to limit the need for more invasive procedures. Thus, when considering management for patients with AUS/FLUS, it is important take into consideration laboratory, clinical, ultrasound findings, and molecular markers to help aid in decision making.

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